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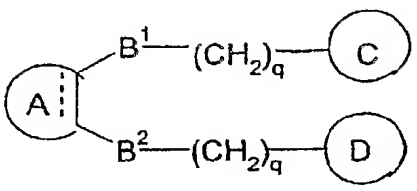
(54) Title: NOVEL COMPOUNDS AS KINASE INHIBITORS



(I)

(57) Abstract: The invention discloses novel compounds of the general formula (I), in which the variables are as defined in the claims, as MAPKAP kinase 2 inhibitors.

NOVEL COMPOUNDS AS KINASE INHIBITORS

FIELD OF THE INVENTION

The invention provides novel compounds, their preparation and use as MAPKAP kinase 2 inhibitors.

BACKGROUND OF THE INVENTION

MAP kinase-activated protein kinase 2 (MAPKAP-K2 or MK2) is one of several kinases downstream to the stress-activated p38 MAP kinase α- and β-isoforms.
The p38 MAP kinase pathway is known to mediate stress responses and is activated by heat shock, UV light, bacterial lipopolysaccharide (LPS) and the pro-inflammatory cytokines TNF-α or IL-1. Activation of this pathway affects cell division, apoptosis, invasiveness of cultured cells and the inflammatory response.
Targeted disruption of the MAPKAP-K2 gene in mice suggest that MAPKAP-K2 is essential for the response to LPS as its absence causes a severe reduction in the biosynthesis of several cytokines, especially TNF-α. (Kotlyarov, A., A. Neininger, C. Schubert, R. Eckert, C. Birchmeier, H. D. Volk, and M. Gaestel. 1999) MAPKAP kinase 2 is essential for LPS-induced TNF-alpha biosynthesis. Nat.Cell Biol **1**:94-97.

Stimulation of cells with stress factors such as microbial pathogens leads to the activation of the p38 kinase pathway and result in the production of pro-inflammatory cytokines. The specific regulation of cytokine translation by the p38 pathway now appears to be mediated by the downstream kinase, MAPKAP-K2. Inhibition of p38 activity has been used to develop a new treatment for inflammatory diseases. The discovery of a role for MAPKAP-K2 in cytokine translation provides a promising new drug target for anti-inflammatory therapy as well as a number of other conditions related to TNF-α and/or p38.

The compounds disclosed in the present invention inhibits Tumour Necrosis Factor (hereinafter TNF), for example TNF-α, and various members of the interleukin family.
Accordingly, the compounds of the invention will be useful in the treatment of diseases or medical conditions in which excessive production of cytokines occur, for example excessive production of TNF-α or interleukins. It is known that cytokines are produced by a variety of cells such as monocytes and macrophages and that they give ride to a variety of physiological effects which are believed to be important in disease or medical conditions such as in-

flammation and immunoregulation. A massive release of TNF-α in the host produces severe damage to a range of tissues. It is therefore clear that TNF-α inhibitors have application in disorders which involve an inflammatory response, but this cytokine has multiple inflammatory, metabolic and immunological activities (Jirillo, E. Pellegrino, N.M. and Antonaci, S. Role of Tumor Necrosis Factor-α in Physiological and Pathological Conditions. *Med. Sci. Res.*, **1995**, *23*, 75-79).

Abnormal levels of TNf-α have been implicated in a large number of different diseases as mentioned in WO99/32110. The disease are arthritic conditions such as rheumatoid arthritis, acute rheumatoid fever, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, psoriatic arthritis, Reiter's syndrome, osteoarthritis, traumatic arthritis, and rubella arthritis; Bacterial and viral/parasitic infections such as in fever, sepsis, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, systemic inflammatory response syndrome, tuberculosis, malaria including Plasmodium falciparum malarie and cerebral malaria, meningitis and infections by Helicobacter pylori during peptic ulcer disease, Chaga's disease, infections from E-coli, Trypanosome, Staphylococcus, meningococcal, Borrelia burgdorferi, cytomegalovirus, influenza virus, Sendai virus, Treponema Pallidum, Theiler's encephalomyelitis virus, viral diseases caused by HIV, CMV and herpes; Bone resorption disease and osteoporosis; Cancers: primary as well as secondary tumors. Cardiovascular diseases such as congestive heart failure and damage following heart disease, cardiomyopathy, myocarditis, vasculitis, atherosclerosis, thrombosis and myalgias; Diseases in the central nervous system such as stroke, acute encephalitis, Alzheimer's disease, Parkinson's disease, ischemia and prevention of neuronal damage following cerebral ischaemia , open and closed head trauma, central nervous system injury, cachexia, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis; Inflammatory bowel diseases such as Crohn's disease, gastritis and ulcerative colitis; Immune related conditions such as graft-versus-host rejection, allograft rejection such as those of the kidney, heart, liver, skin, lung and complications following hip replacement; Ophthalmic diseases such as retinitis, retinopathies, uveitis, ocular photophobia, actue injury to the eye tissue, corneal graft rejection, ocular neovascularisation, retinal neovascularisation, diabetic retinopathy, retrolental febroplasia, neovascular glaucoma. Pulmonary conditions such as asthma, adult respiratory distress syndrom, chronic and acute pulmonary inflammatory disease, chronic obstructive pulmonary disease, lung inflammation, pulmonary sarcosis, pneumonia, restenosis, silicosis, allergic respiratory diseases, alveolar injury; Skin related diases such as psoriasis, eczema, burns, dermatitis, contact dermatitis, keloid formation and scar tissue formation; Liver diseases such as hepatic

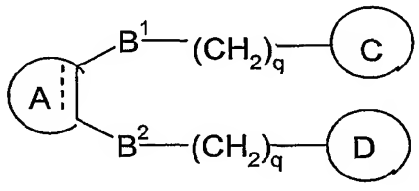
failure, liver disease during acture inflammation, severe alcoholic hepatitis; glomerulonephritis, pyresis, pancreatitis including systemic complications in acute pancreatitis, myelodysplastic syndromes, biliary cirrhosis, nephritis, (cardiac /renal) reperfusion injury, macular degeneration, uveitis, disorders of the female reproductive system, endometriosis, acute synovitis and systemic lupus erythematosus.

The suggestion has been made that TNF-α inhibitors are useful in the treatment of diabetes (Argiles, J.M., Lopez-Soriano, J. and Lopez-Soriano, F.J. Cytokines and Diabetes: The Final Step. Involvement of TNF-α in both Type I and Type II Diabetes Mellitus. *Horm. Metab. Res.*, **1994**, *26*, 447 - 449).

Due to the pharmacological activity of the compounds of the present invention as inhibitors of MAPKAP kinase 2, which in mammalian cells is involved in stress-induced biosynthesis of several pro-inflammatory and inflammatory cytokines (Kotlyarov et. al, Nature cell biology, Vol. 1 (2) pp. 94-97 (1999) Jun) the inhibition of MAPKAP-K2 has potential in the treatment of all diseases that relate to dysregulated cytokine production of which TNF-α is an important proinflammatory cytokine.

SUMMARY OF THE INVENTION

The invention provides novel compounds having of the formula (I)

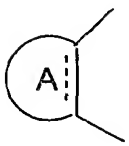


(I)

wherein

each q is independently 0 or 1;

(II)



is cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused arylcycloalkylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylhet-

eroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroarylene, or fused heteroarylheterocyclylene,

optionally substituted with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34}, wherein

R^{31}, R^{32}, R^{33}, and R^{34} independently of each other are alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^1-O-, R^1-S(O)$_m$-, R^1-O-C(O)-, R^1-C(O)-O-, R^1-C(O)-, $N(R^1)(R^2)$-C(O)-, $N(R^1)(R^2)$-, R^1-C(O)-N(R^2)-$(CH_2)_m$-, $B(OR^1)(OR^2)$-, R^1-O-$(CH_2)_n$-, or $N(R^1)(R^2)$-$(CH_2)_n$-, wherein

R^1 and R^2, independently of each other, are hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

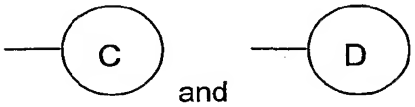
or

R^1 and R^2, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

m is an integer of 0,1, or 2;

n is an integer of 1, 2, or 3; and

---- indicates a single bond, double bond or an aromatic bond;



and

each independently represent a group selected from the following:

cycloalkyl, heterocyclic, aryl, heteroaryl, fused cycloalkylaryl, fused arylcycloalkyl, fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl,

optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38}, wherein

R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are alkyl, halogen,aralkyl, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^3-O-$(CH_2)_w$-, R^3-S(O)$_v$-, $N(R^3)(R^4)$-S(O)$_v$-, $-R^3$-O-C(O)-, R^3-C(O)-O-, R^3-C(O)-, $N(R^3)(R^4)$-C(O)-, R^3-C(O)-N(R^4)-$(CH_2)_w$, $B(OR^3)(OR^4)$-, $N(R^3)(R^4)$-$(CH_2)_w$-, or phenyl optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^5-O-, R^5-S(O)$_s$-, R^5-O-C(O)-, R^5-C(O)-O-, R^5-C(O)-, $N(R^5)(R^6)$-C(O)-, $N(R^5)(R^6)$-, R^5-C(O)-N(R^5)-$(CH_2)_t$, $B(OR^5)(OR^6)$-, R^5-O-$(CH_2)_t$-, or $N(R^5)(R^6)$-$(CH_2)_t$-, wherein

R^3 and R^4, independently of each other, are hydrogen, halogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, or phenyl optionally substituted with

one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $N(R^7)(R^8)$-, or $N(R^7)(R^8)$-$(CH_2)_a$-, wherein

R^7 and R^8, independently of each other, are hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, or cycloalkyl;

and

a is an integer of 1, 2, or 3,

or

R^3 and R^4, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

R^5 and R^6, independently of each other, are hydrogen, halogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

or

R^5 and R^6, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

v and s, independently of each other, are an integer of 0,1, or 2; and

w, r and t, independently of each other, are an integer of 0, 1, 2, or 3;

B^1 and B^2, independently of each other, are a linker selected from the group consisting of –C(X)-, –O-C(X)-, -C(X)-O-, $-N(R^{15})$-C(X)-, -C(X)-$N(R^{15})$-, $-N(R^{15})$-$S(O)_w$-, or $-S(O)_w$-$N(R^{15})$-, wherein

w is an integer of,1, or 2;

X is O, S or H_2; and

R^{15} is hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

The invention also provides a pharmaceutical composition comprising, as an active ingredient, at least one compound according to the above together with one or more pharmaceutically acceptable carriers or excipients.

The invention provides the use of the compounds as above as medicaments.

The invention also provides the use of the compounds as above for the manufacture of a medicament for the treatment of the treatment and/or prevention of disorders or diseases, wherein a MAPKAP kinase 2 interaction is beneficial.

The invention provides a method for the treatment and/or prevention of disorders or diseases, wherein a MAPKAP kinase 2 interaction is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound according to the above or a pharmaceutical composition according to the above.

DEFINITIONS

The term "optionally substituted" as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. When the group in question are substituted with more than one substituent the substituent may be the same or different.

The use of prefixes of this structure: C_{x-y}-alkyl, C_{x-y}-haloalkyl, C_{x-y}-alkenyl, C_{x-y}-alkynyl, C_{x-y}-cycloalkyl, C_{x-y}-aryl, or C_{x-y}-cycloalkyl-C_{x-y}-alkenyl- designates a radical of the designated type having from x to y carbon atoms. If the prefix is used in connection with radicals containing heteroatoms, such as for instance C_{x-y}-heterocyclyl or C_{x-y}-heteroaryl, then one (or more) of the carbon atoms are heteroatoms.

The term "alkyl" as used herein, alone or in combination, refers to a straight or branched chain saturated monovalent hydrocarbon radical having, for instance, from one to ten carbon atoms, for example C_{1-8}-alkyl. Typical C_{1-8}-alkyl groups include, but are not limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-pentyl, n-hexyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C_{1-8}-alkyl" as used herein also includes secondary C_{3-8}-alkyl and tertiary C_{4-8}-alkyl.

The term " alkenyl" as used herein, alone or in combination, refers to a straight or branched chain monovalent hydrocarbon radical having, for instance, from two to ten carbon atoms and at least one carbon-carbon double bond, for example C_{2-8}-alkenyl. Typical C_{2-8}-alkenyl groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "alkynyl" as used herein alone or in combination, refers to a straight or branched monovalent hydrocarbon group containing, for instance, from 2 to the specified number of

carbon atoms and at least one triple carbon-carbon bond, for example C_{2-8}-alkynyl. Typical C_{2-8}-alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "cycloalkyl" as used herein, alone or in combination, refers to a non-aromatic carbocyclic monovalent hydrocarbon radical having, for instance, from three to twelve carbon atoms, and optionally with one or more degrees of unsaturation, for example C_{3-8}-cycloalkyl. Such a ring may be optionally fused to one or more benzene rings or to one or more of other cycloalkyl ring(s). Such a ring may also be bicyclic. Typical C_{3-8}-cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl and the like.

The term "cycloalkylene" as used herein, alone or in combination, refers to a non-aromatic carbocyclic divalent hydrocarbon radical having, for instance, from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, for example C_{3-8}-cycloalkylene. Such a ring may be optionally fused to one or more benzene rings or to one or more of other cycloalkyl ring(s). Such a ring may also be bicyclic. Typical C_{3-8}-cycloalkylene groups include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,2-diyl, cyclohexenyl-1,2-diyl, cycloheptyl-1,4-diyl, cycloheptenyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

The term "heterocyclic ring" or "heterocyclic" or "heterocyclyl" as used herein, alone or in combination, refers to a heterocyclic ring with for instance from 3 to 12 member atoms, such as C_{3-10}-heteroaryl, for instance C_{3-6}-heteroaryl, having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO_2, O, or N, for example C_{3-8}-heterocyclyl. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Such a ring may also be bicyclic. Typical C_{3-8}-heterocyclyl groups include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, piperazine, and the like.

The term "heterocyclylene" as used herein, alone or in combination, refers to a heterocyclic ring diradical with for instance from 3 to 12 member atoms, such as C_{3-10}-heteroaryl, for instance C_{3-6}-heteroaryl, optionally having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO_2, O, or N. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Such a ring may also be bicyclic. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl,

1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, piperazine-1,4-dyil, and the like.

The term "aryl" as used herein refers to a carbocyclic aromatic ring radical or to a aromatic ring system radical such as for instance C_{6-18}-aryl, for instance C_{6-16}-aryl, such as C_{6-14}-aryl. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems.

The term "heteroaryl", as used herein, alone or in combination, refers to a aromatic ring radical with for instance from 5 to 7 member atoms, or to a aromatic ring system radical with for instance from 7 to 18 member atoms, containing one or more heteroatoms selected from nitrogen, oxygen, or sulfur heteroatoms, wherein N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions; such as e.g. furanyl, thienyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, and indazolyl, and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated below.

Examples of "aryl" and "heteroaryl" includes, but are not limited to phenyl, biphenyl, indenyl, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furanyl (2-furanyl, 3-furanyl), indolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, oxatriazolyl, thiatriazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyrazolyl (1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (isoxazo-3-yl, isoxazo-4-yl, isoxaz-5-yl), isothiazolyl (isothiazo-3-yl, isothiazo-4-yl, isothiaz-5-yl) thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridinyl (2-pyridinyl, 3-pyridinyl, 4-pyridinyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolinyl (2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 8-quinolinyl), isoquinolinyl (1-isoquinolinyl, 3-isoquinolinyl, 4-isoquinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 8-isoquinolinyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydrobenzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzob]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, benzo[b]thiophen-4-yl,

benzo[b]thiophen-5-yl, benzo[b]thiophen-6-yl, benzo[b]thiophen-7-yl), 2,3-dihydro-benzo[b]thiophenyl (2,3-dihydro-benzo[b]thiophen-2-yl, 2,3-dihydrobenzo[b]thiophen-3-yl, 2,3-dihydro-benzo[b]thiophen-4-yl, 2,3-dihydro-benzo[b]thiophen-5-yl, 2,3-dihydro-benzo[b]thiophen-6-yl, 2,3-dihydro-benzo[b]thiophen-7-yl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazolyl (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (2-benzoxazolyl, 3-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, 7-benzoxazolyl), benzothiazolyl (2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepinyl (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepinyl (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), benzo[1,3]dioxole (2-benzo[1,3]dioxole, 4-benzo[1,3]dioxole, 5-benzo[1,3]dioxole, 6-benzo[1,3]dioxole, 7-benzo[1,3]dioxole), and tetrazolyl (5-tetrazolyl, N-tetrazolyl).

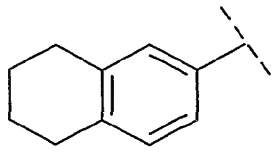
The present invention also relates to partly or fully saturated analogues of the ring systems mentioned above.

The term “arylene”, as used herein, alone or in combination, refers to carbocyclic aromatic ring diradical or to a aromatic ring system diradical. Examples of “arylene” include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, and the like. The term "arylene" alone or in combination also include other divalent radicals of the monovalent radicals mentioned in the definition of aryl.

The term “aralkyl”, as used herein, alone or in combination, refers to aryl as defined above and alkyl as defined above.

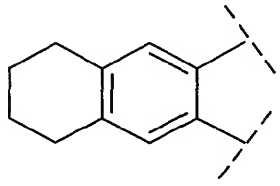
The term “heteroarylene”, as used herein, alone or in combination, refers to a five to seven membered aromatic ring diradical, or to a aromatic ring system diradical, containing one or more heteroatoms selected from nitrogen, oxygen, or sulfur heteroatoms, wherein N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions. Examples of “heteroarylene” used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like. The term "heteroarylene" alone or in combination also include other divalent radicals of the monovalent radicals mentioned in the definition of heteroaryl.

As used herein, the term "fused cycloalkylaryl" refers to a cycloalkyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused cycloalkylaryl" used herein include 5-indanyl, 5,6,7,8-tetrahydro-2-naphthyl,



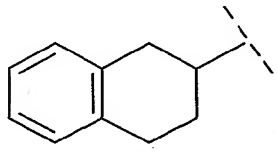
, and the like.

As used herein, the term "fused cycloalkylarylene" refers to a fused cycloalkylaryl, wherein the aryl group is divalent. Examples of "fused cycloalkylarylene" used herein include



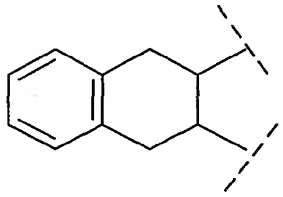
, and the like.

As used herein, the term "fused arylcycloalkyl" refers to an aryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution Examples of "fused arylcycloalkyl" used herein include 1-indanyl, 2-indanyl, 1-(1,2,3,4-tetrahydronaphthyl),



, and the like.

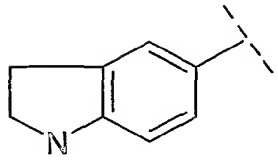
As used herein, the term "fused arylcycloalkylene" refers to a fused arylcycloalkyl, wherein the cycloalkyl group is divalent. Examples of "fused arylcycloalkylene" used herein include



, and the like.

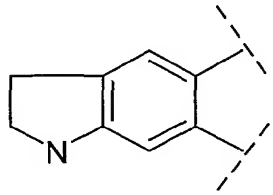
As used herein, the term "fused heterocyclylaryl" refers to a heterocyclyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused heterocyclylaryl" used herein include 3,4-methylenedioxy-1-

phenyl,



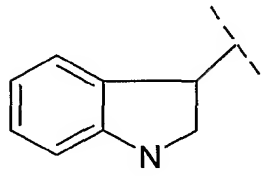
, and the like

As used herein, the term "fused heterocyclylarylene" refers to a fused heterocyclylaryl, wherein the aryl group is divalent. Examples of "fused heterocyclylarylene" used herein include



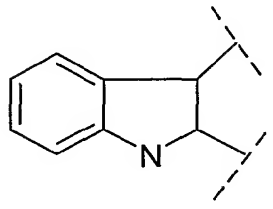
, and the like.

As used herein, the term "fused arylheterocyclyl" refers to an aryl group fused to a heterocyclyl group, the two having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of " fused arylheterocyclyl" used herein include 2-(1,3-benzodioxolyl),



, and the like.

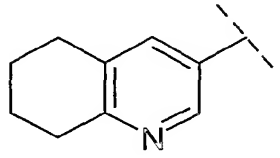
As used herein, the term "fused arylheterocyclylene" refers to a fused arylheterocyclyl, wherein the heterocyclyl group is divalent. Examples of "fused arylheterocyclylene" used herein include



, and the like.

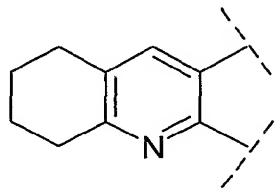
As used herein, the term "fused cycloalkylheteroaryl" refers to a cycloalkyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused cycloalkylheteroaryl" used herein include 5-aza-

6-indanyl,



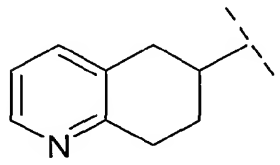
, and the like.

As used herein, the term "fused cycloalkylheteroarylene" refers to a fused cycloalkylheteroaryl, wherein the heteroaryl group is divalent. Examples of "fused cycloalkylheteroarylene" used herein include



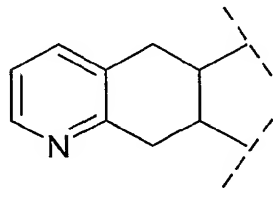
, and the like.

As used herein, the term "fused heteroarylcycloalkyl" refers to a heteroaryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused heteroarylcycloalkyl" used herein include 5-aza-1-indanyl,



and the like.

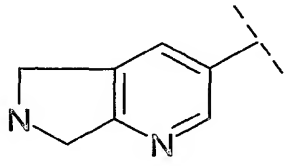
As used herein, the term "fused heteroarylcycloalkylene" refers to a fused heteroarylcycloalkyl, wherein the cycloalkyl group is divalent. Examples of "fused heteroarylcycloalkylene" used herein include



, and the like.

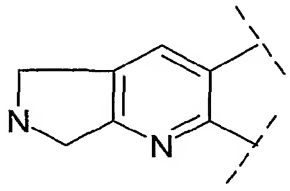
As used herein, the term "fused heterocyclylheteroaryl" refers to a heterocyclyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused heterocyclylheteroaryl" used herein in-

clude 1,2,3,4-tetrahydro-beta-carbolin-8-yl,



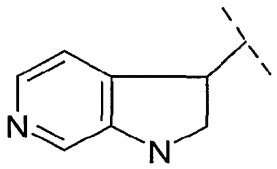
and the like.

As used herein, the term "fused heterocyclylheteroarylene" refers to a fused heterocyclylheteroaryl, wherein the heteroaryl group is divalent. Examples of "fused heterocyclylheteroarylene" used herein include



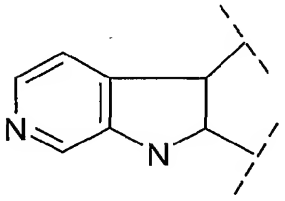
, and the like.

As used herein, the term "fused heteroarylheterocyclyl" refers to a heteroaryl group fused to a heterocyclyl group, the two having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused heteroarylheterocyclyl" used herein include



, and the like.

As used herein, the term "fused heteroarylheterocyclylene" refers to a fused heteroarylheterocyclyl, wherein the heterocyclyl group is divalent. Examples of "fused heteroarylheterocyclylene" used herein include



, and the like.

The term "halogen" or "halo" means fluorine, chlorine, bromine or iodine.

The term "haloalkyl" as used herein means an alkyl substituted with one or more halogen atoms, such as for instance chloromethyl, fluoromethyl, bromomethyl, dichloromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 2,2-difluoroethyl, or 1,2-dichloropropyl.

The term "hydroxyalkyl" as used herein means an alkyl substituted with one or more hydroxy groups, such as for instance 2-hydroxyethyl or 3,3-dihydroxypropyl.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the terms "contain" or "containing" can refer to in-line substitutions at any position along the above defined alkyl, alkenyl, alkynyl or cycloalkyl substituents with one or more of any of O, S, SO, SO_2, N, or N-alkyl, including, for example, $-CH_2-O-CH_2-$, $-CH_2-SO_2-CH_2-$, $-CH_2-NH-CH_3$ and so forth.

Certain of the above defined terms may ocur more than once in the structural formulae, and upon such ocurrence each term shall be defined independently of the other.

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in this invention, a compound of Formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties *in vivo* such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters (*e.g.*, C_{1-4}), lower acyloxyalkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in this invention, a compound of general Formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and also encompasses a) compounds in which the biohydrolyzable functionality in such a prodrug is encompassed in the compound of Formula (I) and b) compounds which may be oxidized or reduced biologically at a given functional group to yield drug substances of For-

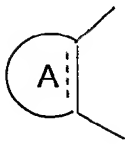
mula (I). Examples of these functional groups include, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

The term "pharmacologically effective amount" or shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount. The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an animal or human that is being sought.

The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the full spectrum of treatments for a given disorder from which the patient is suffering, such as the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

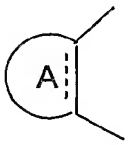
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention compounds as above are provided, wherein



is cycloalkylene, arylene, fused arylcycloalkylene, fused cycloalkylarylene, optionally substituted with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

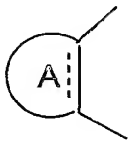
In another embodiment



is heteroarylene, heterocyclylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylheteroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroary-

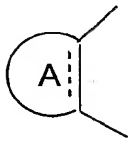
lene, or fused heteroarylheterocyclylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

In another embodiment



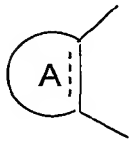
is cycloalkylene, heteroarylene or arylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

In another embodiment



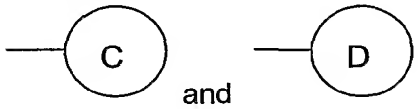
is fused arylcycloalkylene, fused cycloalkylarylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylheteroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroarylene, or fused heteroarylheterocyclylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

In another embodiment



is phenyl, naphtyl or thienyl.

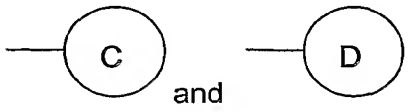
In another embodiment



and

each independently represent a group selected from the following:
cycloalkyl, aryl, fused cycloalkylaryl or fused arylcycloalkyl, optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined above.

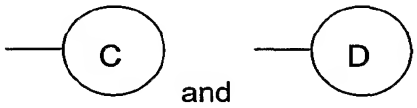
In another embodiment



and

each independently represent a group selected from the following:
heterocyclic, heteroaryl, fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl, optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined above.

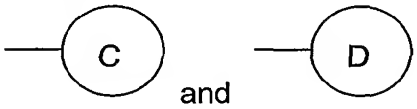
In another embodiment



and

each independently represent a group selected from the following:
heterocyclic, heteroaryl, cycloalkyl or aryl optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined above.

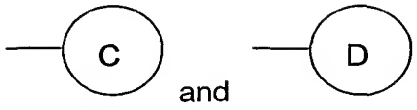
In another embodiment



and

each independently represent a group selected from the following:
fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl, fused cycloalkylaryl or fused arylcycloalkyl, optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined above.

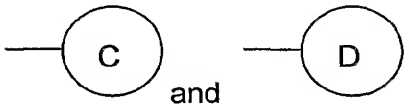
In another embodiment



and

each independently represent a group selected from the following:
aryl or heteroaryl optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined above.

In another embodiment



and

are selected from phenyl, naphtyl, thienyl, thiazolyl or pyridyl;

In another embodiment R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are alkyl, halogen, aralkyl, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^3-O-$(CH_2)_w$-, R^3-S(O)$_v$-, N(R^3)(R^4)-S(O)$_v$-, -R^3-O-C(O)-, R^3-C(O)-O-, R^3-C(O)-, wherein R^3 and R^4, v and w are as defined above.

In another embodiment R^3 and R^4 are independently selected from hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, or R^3 and R^4, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

In another embodiment R^3 and R^4 are hydrogen or alkyl;

In another embodiment R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are N(R^3)(R^4)-C(O)-, R^3-C(O)-N(R^4)-$(CH_2)_w$, B(OR^3)(OR^4)-, N(R^3)(R^4)-$(CH_2)_w$-, or phenyl optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^5-O-, R^5-S(O)$_s$-, R^5-O-C(O)-, R^5-C(O)-O-, R^5-C(O)-, N(R^5)(R^6)-C(O)-, N(R^5)(R^6)-, R^5-C(O)-N(R^5)-$(CH_2)_t$, B(OR^5)(OR^6)-, R^5-O-$(CH_2)_t$-, or N(R^5)(R^6)-$(CH_2)_t$-, wherein R^3, R^4, R^5, R^6, w, s and t are as defined above.

In another embodiment B^1 and B^2, independently of each other, are a linker selected from the group consisting of –C(X)-, –O-C(X)-, -C(X)-O-, -N(R^{15})-C(X)-, -C(X)-N(R^{15})-, wherein X is O, S and R^{15} is as defined above.

In another embodiment B^1 and B^2 independently of each other, are selected from –C(O)-, –O-C(O)-, -C(O)-O-, -N(R^{15})-C(O)- or -C(O)-N(R^{15})-, wherein R^{15} is as defined above.

In another embodiment R^{15} is hydrogen, hydroxyalkyl, alkyl, alkenyl or alkynyl;

In another embodiment R^{15} is hydrogen or alkyl;

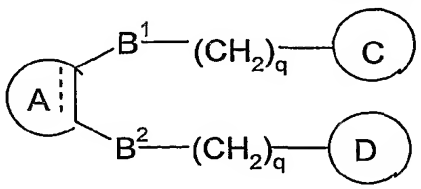
In another embodiment the invention provides compounds such as
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid methyl ester

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 3-carboxy-naphthalen-2-yl ester.

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 2-(3-carboxy-naphtaleneoxycarbonyl) naphtyl ester
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid
2-(4-Dipropylsulfamoyl-benzoylamino)-benzoic acid
2-[(4-Dipropylsulfamoyl-benzoyl)-methyl-amino]-benzoic acid
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 2,4,6-trimethoxy-benzylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 4-methanesulfonyl-benzylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-2-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-3-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-4-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid benzylamide
2-(4-methoxy-benzoylamino)-N-(2-thiazolyl)-benzamide
3-(4-Methoxy-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide
Pyridine-2-carboxylic acid [3-(thiazol-2-ylcarbamoyl)-naphthalen-2-yl]-amide

Pyridine-2-carboxylic acid {3-[(naphthalen-1-ylmethyl)-carbamoyl]-naphthalen-2-yl}-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-benzene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide
Pyridine-2-carboxylic acid {2-[(naphthalen-1-ylmethyl)-carbamoyl]-phenyl}-amide
4-({[3-(4-Methoxy-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester
4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester
4-[({3-[(Pyridine-2-carbonyl)-amino]-thiophene-2-carbonyl}-amino)-methyl]-benzoic acid methyl ester
4-({[4-(4-Methoxy-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester
4-({[4-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester
4-[({4-[(Pyridine-2-carbonyl)-amino]-thiophene-3-carbonyl}-amino)-methyl]-benzoic acid methyl ester
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid
N-(3-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-carbonyl}-naphthalen-2-yl)-4-dipropylsulfamoyl-benzamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-2-yl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid [1-(4-methoxy-phenyl)-ethyl]-amide
4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester
4-Dipropylsulfamoyl-N-{3-[4-(1-phenyl-ethyl)-piperazine-1-carbonyl]-naphthalen-2-yl}-benzamide or
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide

The present invention provides compounds of the general formula (I)



(III)

wherein the substituents are as defined and are clear from the appended claims.

The present compounds may have one or more asymmetric centres and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoisomers or racemic mixtures thereof, are included in the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

The compound may also be administered to a patient in need thereof in combination with one or more further active substances in any suitable ratios.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising as an active ingredient, at least one compound compound, preferably in a pharmacologically effective amount, more preferably in a therapeutically effective amount, according to the present invention together with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of a compound according to the present invention.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the present invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as hard or soft capsules, tablets, troches, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, aqueous or oily suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg. For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration. The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. Examples are an acid addition salt of a compound having the utility of a free base and a base addition salt of a compound having the utility of a free acid. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. When a compound according to the present invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable acid. When a compound according to the present invention contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable base. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the present invention and these form a further aspect of the present invention.

For parenteral administration, solutions of a compound according to the present invention in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl mono-

stearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the present invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, incorporated herein by reference, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation

products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alchol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the present invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectible aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition,

sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the present invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the present invention are contemplated. For the purpose of this application, topical applications shall include mouth washes and gargles.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the present invention.

Thus, in a further embodiment, there is provided a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or prodrug therof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Lactosum Ph. Eur.	67.8 mg
Cellulose, microcryst. (Avicel)	31.4 mg
Amberlite® IRP88*	1.0 mg

Magnesii stearas Ph. Eur.		q.s.
Coating:		
Hydroxypropyl methylcellulose	approx.	9 mg
Mywacett 9-40 T**	approx	0.9 mg
* Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.		
** Acylated monoglyceride used as plasticizer for film coating.		

If desired, the pharmaceutical composition of the present invention may comprise a compound according to the present invention in combination with further active substances such as those described in the foregoing.

EXAMPLES

HPLC-MS (Method A)

The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G1315A DAD diode array detector
- Hewlett Packard series 1100 MSD
- Sedere 75 Evaporative Light Scattering detector

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis is performed at 40°C by injecting an appropriate volume of the sample (preferably 1 µl) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are giving in the following table.

Column: Waters Xterra MS C-18 X 3 mm id 5 □m

Gradient: 5% - 100% acetonitrile linear during 7.5 min at 1.5ml/min

Detection: 210 nm (analogue output from DAD (diode array detector))

ELS (analogue output from ELS)

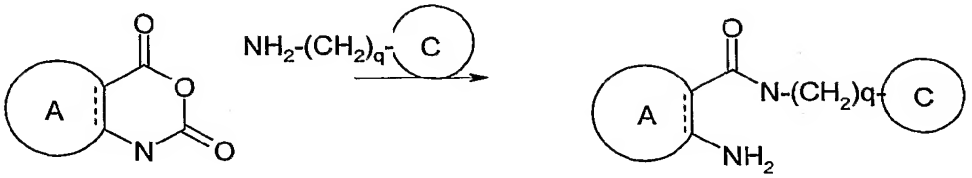
MS ionisation mode API-ES

Scan 100-1000 amu step 0.1 amu

After the DAD the flow is divided yielding approx 1 ml/min to the ELS and 0.5 ml/min to the MS.

General procedure (A)

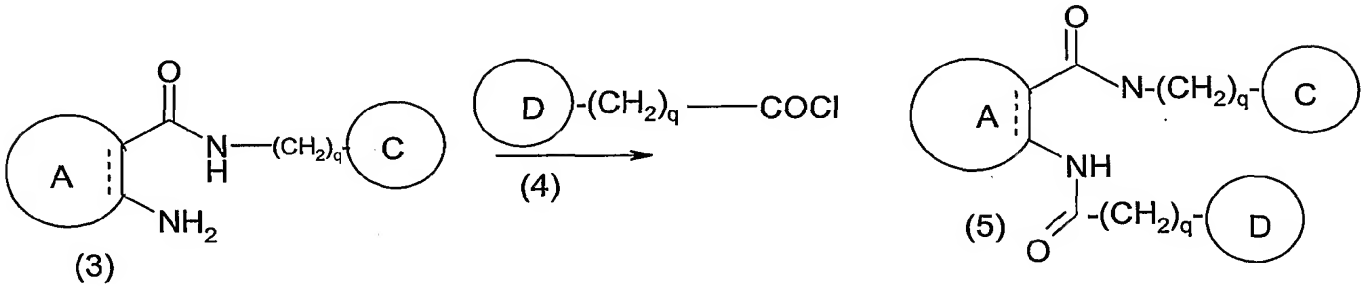
Step A :



(1) (2) (3)

A mixture of a compound of the general formula (1) and a compound of the general formula (2) in toluene is heated at reflux for 6 hours. After cooling the crystals are filtered and washed with toluene, diethylether and dried. The isolated compound of the general formula (3) is used without further purification in step B.

Step B:



(3) (4) (5)

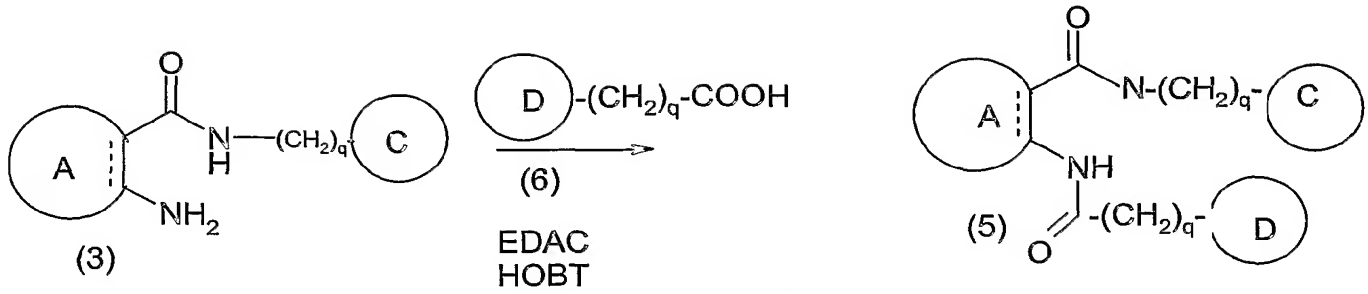
To a solution of a compound of the general formula (3) in tetrahydrofuran a compound of the general formula (4) and triethylamine are added. The reaction mixture is stirred at room temperature for 1 hour, or until TLC indicated the disappearance of starting material. Compounds synthesised by this method are purified by quenching with water and filtration followed by a crystallisation with an organic solvent.

General procedure (B)

Step A:

As described for the general procedure (A), step A

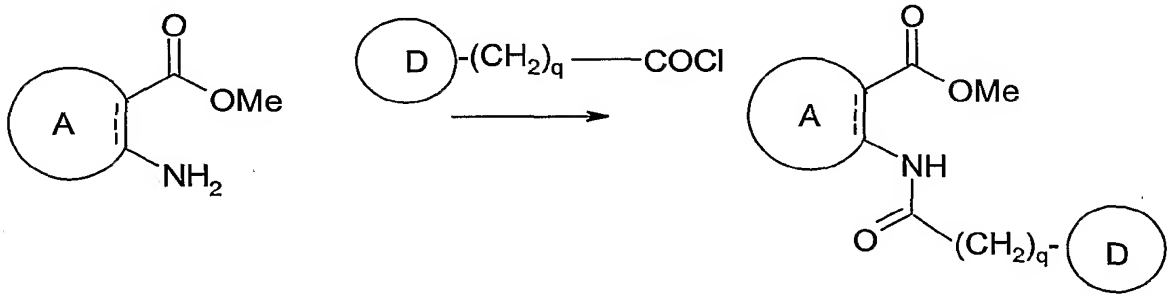
Step B:



To a solution of compound of the general formula (6) in DMF, 1.5 molar equivalent of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1 molar equivalent of hydroxybenzotriazole are added. The reaction mixture is stirred at room temperature for 0.5 hour, whereupon a compound of the general formula (3) and triethylamine 1 equivalent are added. The reaction mixture is stirred at room temperature overnight. The compounds synthesised by this general procedure is purified by aqueous work-up followed by crystallisation from an organic solvent.

General procedure (C)

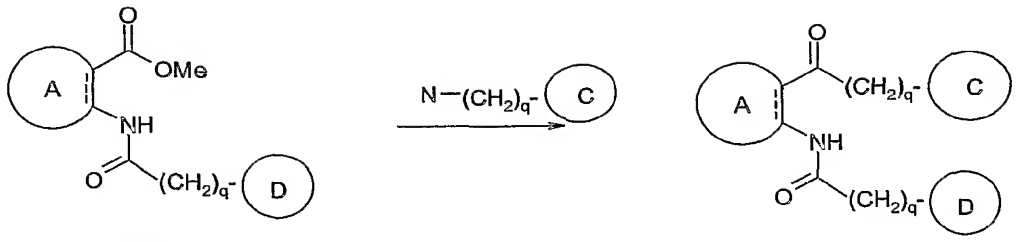
Step A:



(7) (8)

To a solution of a compound of the general formula (7) (1 mmol) in tetrahydrofuran (10 ml), an acid chloride (1.1 – 1.5 mmol) or an acid chloride hydrochloride (1.1 – 1.5 mmol) and triethylamine (1.1 – 3.1 mmol) are added. The reaction mixture is stirred at room temperature for 2 hours. The mixture is concentrated *in vacuo* and stirred with 10 ml H_2O for 5 min. The separated compound is filtered off, washed with H_2O and dried. The isolated materiel of the general formula (8) is used without further purification in step B.

Step B

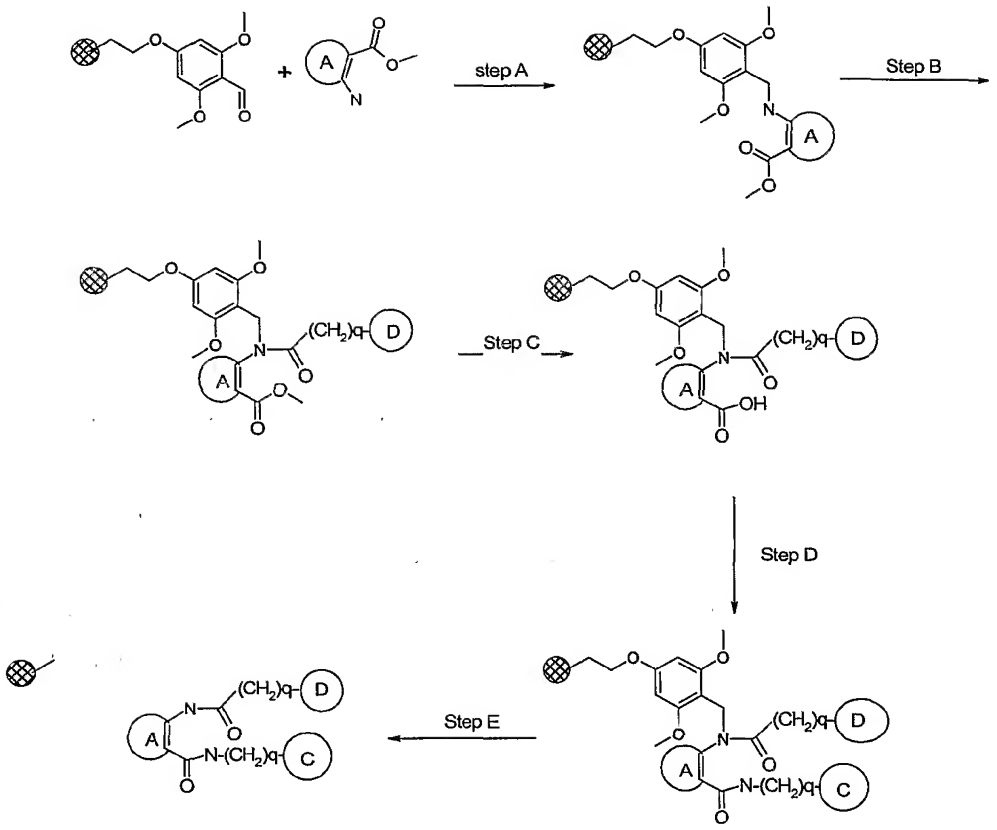


(8) (9)

To a mixture of a compound of the general formula (8) (1 mmol) and C-amine (1.1 mmol) in dry dimethylformamide (5 ml) potassium tert-butoxide (1.1 mmol) is added. The reaction mixture is heated at 60°C and the reaction is followed by TLC (EtOAc) until completion. After cooling the mixture is concentrated *in vacuo*, redissolved in 20 ml EtOAc and washed with 3x20 ml 1N NaOH. The organic layer is dried with Na_2SO_4, filtered and concentrated *in vacuo*. The compound of the general formula (9) is either stirred in 5 ml ether, filtered off and then washed with H_2O, or purified by Prep-HPLC (eluent H_2O:CH_3CN as gradient from 95/5 -> 0/100).

General procedure D:

Solid phase synthesis:



Step A: Reductive amination of Barany-type linker

To 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene (60 mg or less, 0.55 mmol/g) are added in the order given a solution of the primary amine (0.6 mmol) in a mixture of NMP, NaCNBH3 (0.6 ml of a 1 mol/l solution in NMP/MeOH: 7/3), and acetic acid (0.12 ml). The mixture is shaken at room temperature for 16 hours and then washed with methanol (1 x 1.5 ml) and NMP (2 x 1.5 ml).

Step B: Acylation of resin bound amine

To the resin bound amine a solution of the acid chloride (0.64 mmole, 0.8 ml of a 0.6 mol/l solution in NMP) is added, followed by the addition of DIPEA (0.136 ml. The resulting mixture is shaken at room temperature for 15 hours, the washed with (5 x 1.0 ml) NMP

Step C: Methylester cleavage.

To the resin bound methylester potassium THF 1.0 ml was added followed by trimethylsilanolate (0.5 ml, 0.24 mol/l in THF). The mixture is shaken at room temperature for 2 hours then washed with DMF (3 x 1.5 ml), 30% acetic acid in THF (1 ml), DMF (3 x 1 ml) and finally DCM (2 x 1.0 ml)

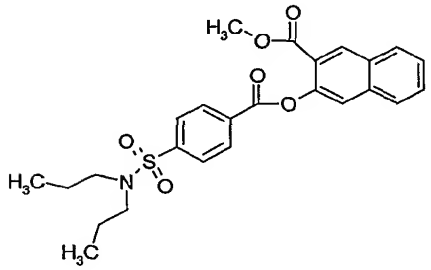
Step D : To the resin bound carboxylic acid the amine (0.8 ml, 0.6 mol/l in NMP) was added, followed by DIPEA (0.136 ml) and PyBroP (0.4 ml, 1.0 mol/l in NMP). The mixture was shaken at room temperature for 16 hours then washed with NMP (5 x 1ml) and DCM (5 x 1ml)

Step E : Cleavage in 50 % TFA in DCM, 2- 5 hours

Examples:

Example 1 (General procedure (C))

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid methyl ester

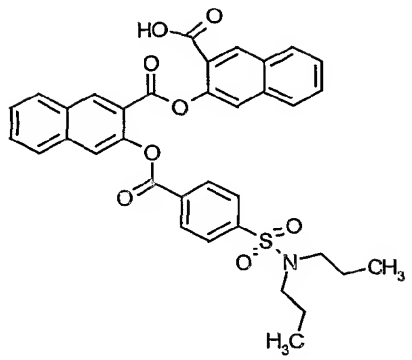


The title compound was prepared from methyl 3-hydroxy-2-naphthoate and 4-dipropylsulfamoyl-benzoyl chloride in 70 % yield.

^{1}H NMR (300 MHz, CDCL3) δ ppm 0.91 (t, *J*=7.35 Hz, 6 H) 1.60 (m, 4 H) 3.15 (m, 4 H) 3.82 (s, 3 H) 7.26 (s, 1 H) 7.60 (m, 2 H) 7.68 (s, 1 H) 7.86 (d, *J*=7.91 Hz, 1 H) 7.98 (d, *J*=8.29 Hz, 3 H) 7.98 (d, 2 H) 8.39 (d, *J*=8.67 Hz, 2 H) 8.68 (s, 1 H)

Example 2 (General procedure (A)) –

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 3-carboxy-naphthalen-2-yl ester.

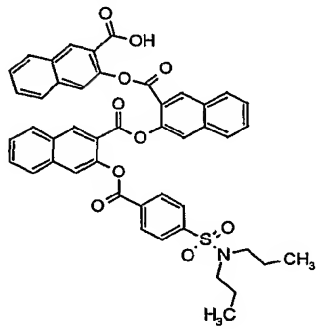


The title compound was prepared from 3-hydroxy-2-naphthoic acid and 4-dipropylsulfamoyl-benzoyl chloride in 5% yield. The title compound was purified by column chromatography.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.81 (t, 6 H) 1.49 (m, 4 H) 2.98 (m, 4 H) 7.60 (m, 4 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 7.80 (d, *J*=7.54 Hz, 1 H) 7.83 (d, *J*=8.67 Hz, 2 H) 7.88 (d, *J*=8.29 Hz, 1 H) 7.92 (d, *J*=7.91 Hz, 1 H) 8.01 (d, *J*=8.29 Hz, 1 H) 8.31 (d, *J*=8.67 Hz, 2 H) 8.64 (s, 1 H) 8.99 (s, 1 H)

Example 3 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 2-(3-carboxy-naphtaleneoxycarbonyl) naphtyl ester

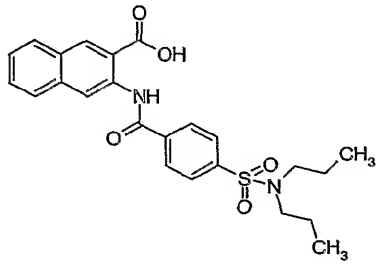


The title compound was prepared from 3-hydroxy-2-naphthoic acid and 4-dipropylsulfamoyl-benzoyl chloride in 2 % yield. The title compound was purified by column chromatography.

^{1}H NMR (300 MHz, $CDCL_3$) δ ppm 0.81 (t, 6 H) 1.50 (m, 4 H) 2.98 (m, 4 H) 7.56 (m, 8 H) 7.69 (s, 1 H) 7.89 (m, 8 H) 8.34 (d, 2 H) 8.61 (s, 1 H) 8.88 (s, 1 H) 9.00 (s, 1 H)

Example 4 (General procedure (C))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid

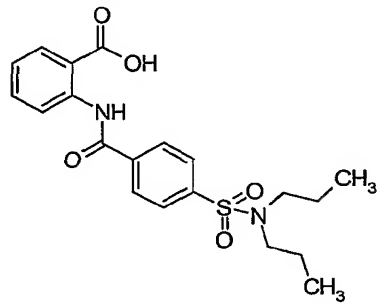


The title compound was prepared from 3-amino-2-naphthoic acid and 4-dipropylsulfamoyl-benzoyl chloride in 31 % yield.

^{1}H NMR (DMSO-d_6): ppm 0.82 (t, 6 H) 1.49 (m, 4 H) 3.08 (t, 4 H) 7.38 (t, *J*=7.35 Hz, 1 H) 7.48 (t, *J*=7.35 Hz, 1 H) 7.82 (d, *J*=7.91 Hz, 1 H) 7.89 (d, *J*=7.91 Hz, 1 H) 7.98 (d, *J*=7.91 Hz, 1 H) 8.26 (d, *J*=8.29 Hz, 2 H) 8.61 (s, 1 H) 9.09 (s, 1 H) 16.32 (s, 1 H); HPLC-MS (Method A): *m/z* = 455 (M+1); R_t = 4.8 min.

Example 5 (General procedure (C))

2-(4-Dipropylsulfamoyl-benzoylamino)-benzoic acid

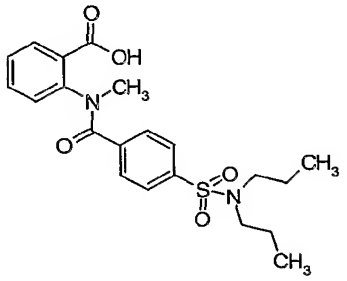


The title compound was prepared from 2-aminobenzoic acid and 4-dipropylsulfamoyl-benzoyl chloride in 55 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.75 (t, 6 H) 1.49 (m, 4 H) 3.08 (t, 4 H) 7.38 (t, *J*=7.25 Hz, 1 H) 7.65 (t, *J*=7.35 Hz, 1 H) 7.04 (d, *J*=8.29 Hz, 2 H) 8.08 (d, *J*=8.29 Hz, 1 H) 8.14 (d, *J*=7.91 Hz, 2 H) 8.26 (d, *J*=8.29 Hz, 1 H) 12.25 (s, 1 H) 13.88 (s, 1 H) 1; HPLC-MS (Method A): *m/z* = 405 (M+1); R_t = 4.4 min.

Example 6 (General procedure (A))

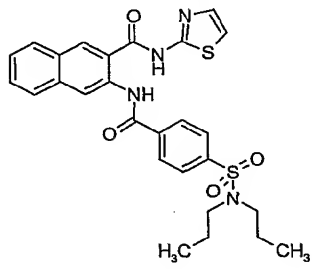
2-[(4-Dipropylsulfamoyl-benzoyl)-methyl-amino]-benzoic acid



The title compound was prepared from 2-methylaminobenzoic acid and 4-dipropylsulfamoyl-benzoyl chloride in 47 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.73 (t, J=7.35 Hz, 6 H) 1.04 (t, J=6.03 Hz, 3 H) 1.32 (m, 4 H) 2.93 (m, 4 H) 7.30 (d, J=7.54 Hz, 1 H) 7.35 (d, J=8.67 Hz, 2 H) 7.44 (d, J=6.78 Hz, 1 H) 7.51 (d, J=7.16 Hz, 1 H) 7.55 (d, J=8.29 Hz, 1 H) 7.69 (m, 1 H) 13.12 (m, 1 H).**Example 7** (General procedure (C))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide



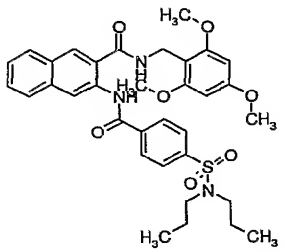
Step A: The intermediate 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester was prepared from methyl 3-amino-2-naphthoate and 4-dipropylsulfamoyl-benzoyl chloride in 96 % yield.

Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 2-aminothiazol in 51 % yield

^{1}H NMR (DMSO-d_6): ppm 0.83 (t, J=7.35 Hz, 6 H) 1.50 (m, 4 H) 3.09 (m, 4 H) 7.28 (d, J=3.39 Hz, 1 H) 7.61 (m, 3 H) 8.00 (m, 4 H) 8.18 (d, J=7.91 Hz, 2 H) 8.62 (m, 2 H) 11.57 (m, 1 H) 12.96 (m, 1 H); HPLC-MS (Method A): m/z = 537 (M+1); R_t = 5.1 min.

Example 8 (General procedure (C))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 2,4,6-trimethoxy-benzylamide

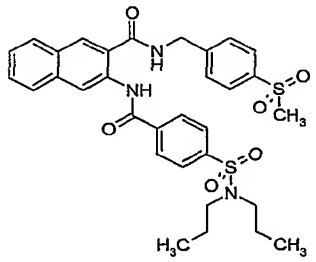


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 2,4,6-trimethoxybenzylamine hydrochloride in 30 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.84 (t, J=7.35 Hz, 6 H) 1.51 (m, 4 H) 3.10 (m, 4 H) 3.76 (s, 6 H) 3.79 (s, 3 H) 4.48 (d, J=4.14 Hz, 2 H) 6.27 (s, 2 H) 7.55 (m, J=24.87, 7.91 Hz, 2 H) 7.91 (m, J=8.48, 8.48 Hz, 2 H) 8.06 (d, J=8.29 Hz, 1 H) 8.16 (d, 2 H) 8.42 (s, 1 H) 8.80 (t, 1 H) 9.05 (s, 1 H) 12.66 (s, 1 H); HPLC-MS (Method A): m/z = 634 (M+1); R_t = 5.5 min.

Example 9 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 4-methanesulfonyl-benzylamide

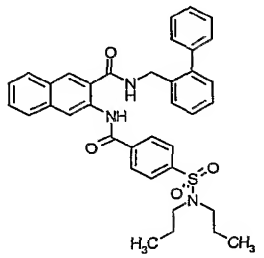


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 4-methylsulphonylbenzylamine hydrochloride in 9 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.82 (t, J=7.33 Hz, 6 H) 1.49 (m, 4 H) 3.08 (m, 4 H) 3.20 (s, 3 H) 4.69 (d, J=5.56 Hz, 2 H) 7.56 (t, J=7.58 Hz, 1 H) 7.66 (m, 3 H) 7.92 (d, J=8.08 Hz, 2 H) 7.99 (m, J=17.43, 8.34 Hz, 4 H) 8.12 (d, J=8.08 Hz, 2 H) 8.57 (s, 1 H) 9.03 (s, 1 H) 9.78 (t, J=5.81 Hz, 1 H) 12.34 (s, 1 H); HPLC-MS (Method A): m/z = 622 (M+1); R_t = 4.9 min.

Example 10 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-2-ylmethyl)-amide

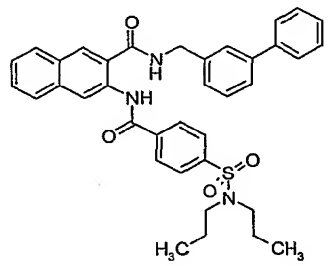


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 2-phenylbenzylamine in 17 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (t, J=7.35 Hz, 6 H) 1.50 (m, 4 H) 3.09 (m, 4 H) 4.54 (d, J=4.90 Hz, 2 H) 7.34 (m, 8 H) 7.54 (m, 2 H) 7.63 (t, J=7.16 Hz, 1 H) 7.94 (m, J=7.91 Hz, 2 H) 8.01 (d, J=8.29 Hz, 2 H) 8.11 (m, 2 H) 8.42 (s, 1 H) 9.01 (s, 1 H) 9.46 (t, J=5.09 Hz, 1 H) 12.33 (s, 1 H); HPLC-MS (Method A): m/z = 620 (M+1); R_t = 5.9 min.

Example 11 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-3-ylmethyl)-amide

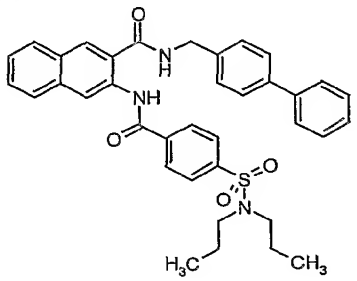


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 3-phenylbenzylamine in 41 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (t, J=7.35 Hz, 6 H) 1.50 (m, 4 H) 3.09 (m, 4 H) 4.64 (d, J=4.90 Hz, 2 H) 7.50 (m, 11 H) 8.00 (m, 4 H) 8.12 (d, 2 H) 8.52 (s, 1 H) 9.01 (s, 1 H) 9.70 (t, J=5.09 Hz, 1 H) 12.43 (s, 1 H); HPLC-MS (Method A): m/z = 620 (M+1); R_t = 5.7 min.

Example 12 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-4-ylmethyl)-amide

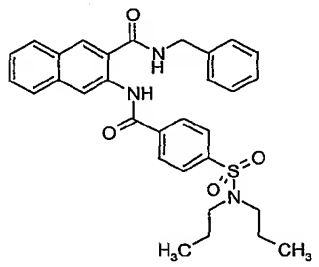


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 4-phenylbenzylamine in 87 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.81 (t, J=7.35 Hz, 6 H) 1.48 (m, 4 H) 3.05 (q, J=7.28 Hz, 4 H) 4.63 (d, J=5.65 Hz, 2 H) 7.49 (m, 11 H) 7.99 (m, 4 H) 8.14 (d, 2 H) 8.56 (s, 1 H) 9.05 (s, 1 H) 9.73 (t, J=5.84 Hz, 1 H) 12.44 (s, 1 H); HPLC-MS (Method A): m/z = 620 (M+1); R_t = 5.9 min.

Example 13 (General procedure (A))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid benzylamide

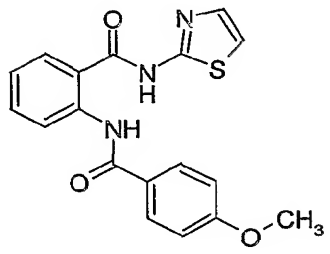


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and benzylamine in 78 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (t, J=7.33 Hz, 6 H) 1.50 (m, 4 H) 3.08 (m, 4 H) 4.59 (d, J=5.56 Hz, 2 H) 7.33 (m, 5 H) 7.55 (t, J=7.33 Hz, 1 H) 7.64 (t, J=7.58 Hz, 1 H) 7.99 (m, 4 H) 8.13 (d, J=8.59 Hz, 2 H) 8.54 (s, 1 H) 9.05 (s, 1 H) 9.70 (t, J=5.56 Hz, 1 H) 12.43 (s, 1 H) ; HPLC-MS (Method A): m/z = 544 (M+1); R_t = 5.4 min.

Example 14 (General procedure (D))

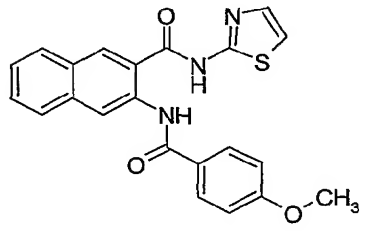
2-(4-methoxy-benzoylamino)-N-(2-thiazolyl)-benzamide



^{1}H NMR ($CDCl_3$): δ ppm 3.90 (s, 3 H) 7.03 (m, 3 H) 7.13 (t, 1 H) 7.30 (d, 1 H) 7.60 (t, *J*=8.10 Hz, 1 H) 7.83 (d, *J*=8.29 Hz, 1 H) 8.04 (d, *J*=9.04 Hz, 2 H) 8.88 (d, *J*=8.67 Hz, 1 H) 11.69 (s, 1 H).

Example 15 (General procedure (D))

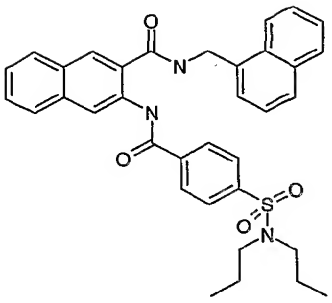
3-(4-Methoxy-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide



^{1}H NMR ($CDCl_3$): δ ppm 3.91 (s, 3 H) 7.05 (m, *J*=9.61, 2.45 Hz, 3 H) 7.37 (t, 1 H) 7.53 (t, *J*=6.97 Hz, 1 H) 7.69 (d, *J*=8.67 Hz, 1 H) 7.80 (d, *J*=8.29 Hz, 1 H) 8.06 (d, *J*=8.67 Hz, 1 H) 8.36 (s, 1 H) 9.26 (s, 1 H) 11.48 (s, 1 H).

Example 16 (General procedure (c))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide

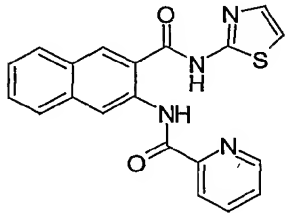


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 1-naphthalenemethylamine in 41 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.82 (t, 6 H) 1.49 (m, 4 H) 3.08 (m, 4 H) 5.06 (d, J=5.65 Hz, 2 H) 7.56 (m, 7 H) 7.96 (m, 5 H) 8.20 (m, 3 H) 8.53 (s, 1 H) 9.04 (s, 1 H) 9.72 (t, J=5.46 Hz, 1 H) 12.41 (s, 1 H); HPLC-MS (Method A): m/z = 594 (M+1); R_t = 5.8 min.

Example 17 (General procedure (D))

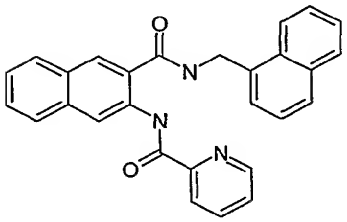
Pyridine-2-carboxylic acid [3-(thiazol-2-ylcarbamoyl)-naphthalen-2-yl]-amide



HPLC-MS (Method A): m/z = 375 (M+1); R_t = 3.6 min.

Example 18 (General procedure (D))

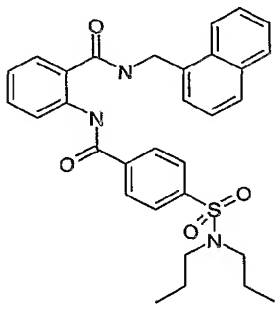
Pyridine-2-carboxylic acid {3-[(naphthalen-1-ylmethyl)-carbamoyl]-naphthalen-2-yl}-amide



HPLC-MS (Method A): m/z = 432 (M+1); R_t = 4.5 min.

Example 19 (General procedure (D))

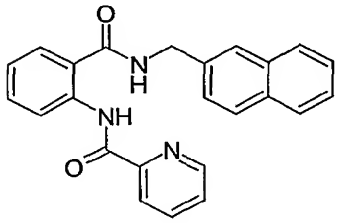
3-(4-Dipropylsulfamoyl-benzoylamino)-benzene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide



HPLC-MS (Method A): *m/z* = 544 (M+1); R_t = 5.2 min.

Example 20 (General procedure (D))

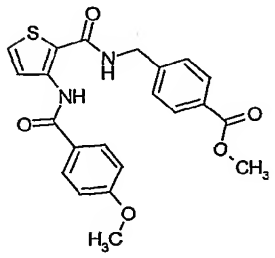
Pyridine-2-carboxylic acid {2-[(naphthalen-1-ylmethyl)-carbamoyl]-phenyl}-amide



HPLC-MS (Method A): *m/z* = 382 (M+1); R_t = 4.0 min.

Example 21 (General procedure (D))

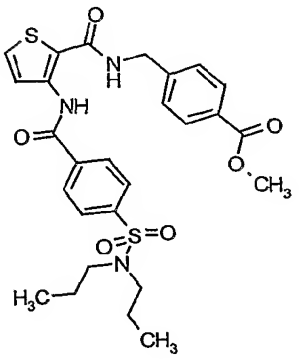
4-({[3-(4-Methoxy-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 425 (M+1); R_t = 4.2 min.

Example 22 (General procedure (D))

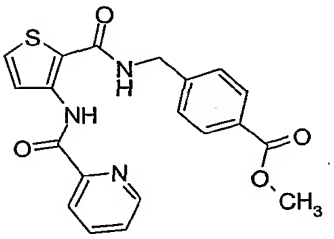
4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 558 (M+1); R_t = 5.0 min.

Example 23 (General procedure (D))

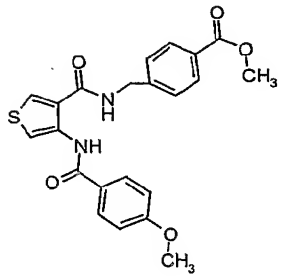
4-[({3-[(Pyridine-2-carbonyl)-amino]-thiophene-2-carbonyl}-amino)-methyl]-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 396 (M+1); R_t = 3.7 min.

Example 24 (General procedure (D))

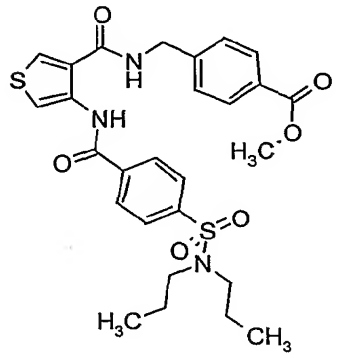
4-({[4-(4-Methoxy-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 425 (M+1); R_t = 3.9 min.

Example 25 (General procedure (D))

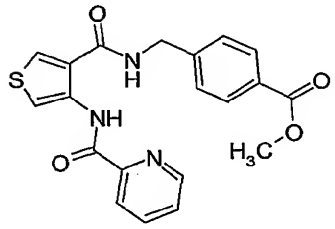
4-({[4-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 558 (M+1); R_t = 4.9 min.

Example 26 (General procedure (D))

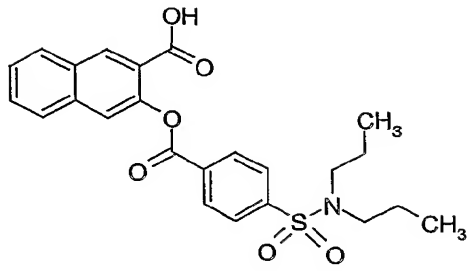
4-[({4-[(Pyridine-2-carbonyl)-amino]-thiophene-3-carbonyl}-amino)-methyl]-benzoic acid methyl ester



HPLC-MS (Method A): *m/z* = 396 (M+1); R_t = 4.1 min.

Example 27 (General procedure (D))

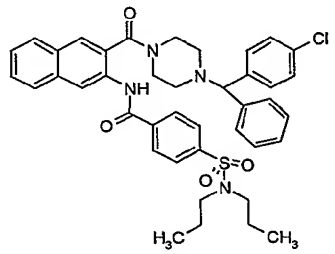
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid



^{1}H NMR ($CDCl_3$): δ ppm 0.89 (t, 6 H) 1.57 (m, 4 H) 3.16 (m, 4 H) 7.58 (t, 1 H) 7.65 (t, *J*=6.78 Hz, 1 H) 7.69 (s, 1 H) 7.86 (d, *J*=7.54 Hz, 1 H) 7.98 (d, *J*=8.29 Hz, 1 H) 7.98 (d, *J*=8.29 Hz, 2 H) 8.36 (d, *J*=8.67 Hz, 2 H) 8.73 (s, 1 H);.

Example 28 (General procedure (D))

N-(3-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-carbonyl}-naphthalen-2-yl)-4-dipropylsulfamoyl-benzamide

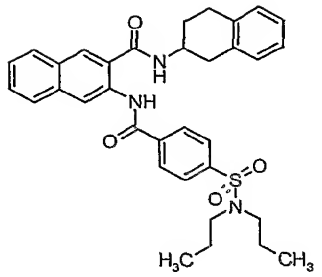


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 1-(4-chlorobenzhydryl)-piperidine in 37 % yield

^{1}H NMR (DMSO-d_6): δ ppm 0.84 (t, *J*=7.16 Hz, 6 H) 1.52 (m, 4 H) 2.33 (m, 4 H) 3.10 (m, 4 H) 3.46 (m, 2 H) 3.60 (m, 2 H) 4.31 (s, 1 H) 7.13-7.63 (m, 11 H) 7.86-8.16 (m, 8 H) 10.62 (s, 1 H); HPLC-MS (Method A): *m/z* = 724 (M+1); R_t = 4.8 min.

Example 29 (General procedure (D))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-2-yl)-amide

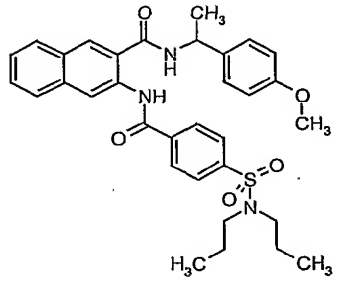


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 3-amino-1,2,3,4-tetrahydro-naphthalene in 39 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.84 (t, J=7.16 Hz, 6 H) 1.52 (m, 4 H) 2.33 (m, 4 H) 3.10 (m, 4 H) 3.46 (m, 2 H) 3.60 (m, 2 H) 4.31 (s, 1 H) 7.13-7.63 (m, 11 H) 7.86-8.16 (m, 8 H) 10.62 (s, 1 H); HPLC-MS (Method A): m/z = 584 (M+1); R_t = 6.1 min.

Example 30 (General procedure (D))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid [1-(4-methoxy-phenyl)-ethyl]-amide

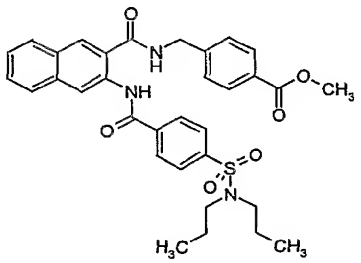


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 1-(4-methoxyphenyl)ethylamine in 39 % yield.

^{1}H NMR ($CDCl_3$): δ ppm 0.89 (t, J=7.35 Hz, 6 H) 1.57 (m, 4 H) 1.68 (d, J=6.78 Hz, 3 H) 3.12 (m, 4 H) 3.81 (s, 3 H) 5.34 (m, 1 H) 6.74 (d, J=7.54 Hz, 1 H) 6.91 (d, J=3.01 Hz, 2 H) 7.39 (d, J=8.67 Hz, 2 H) 7.44 (m, 1 H) 7.55 (t, J=6.97 Hz, 1 H) 7.77 (d, J=7.91 Hz, 1 H) 7.86 (d, J=8.29 Hz, 1 H) 7.93 (d, J=8.29 Hz, 2 H) 8.02 (s, 1 H) 8.13 (d, J=8.29 Hz, 2 H) 9.21 (s, 1 H) 12.11 (s, 1 H); HPLC-MS (Method A): m/z = 584 (M+1); R_t = 6.1 min.

Example 31 (General procedure (D))

4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester

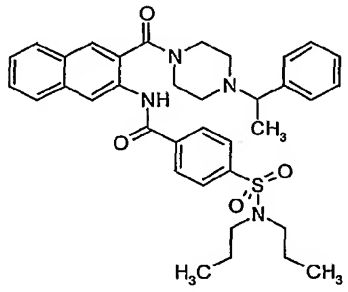


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and methyl 4-(aminomethyl)benzoate in 45 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (t, 3 H) 1.50 (m, 4 H) 3.07 (m, 4 H) 3.84 (s, 3 H) 4.66 (d, J=5.28 Hz, 2 H) 7.55 (d, J=8.29 Hz, 1 H) 7.55 (d, J=8.29 Hz, 2 H) 7.64 (m, 1 H) 7.98 (m, 7 H) 8.10 (d, 2 H) 8.55 (s, 1 H) 9.02 (s, 1 H) 9.76 (t, 1 H) 12.30 (s, 1 H); HPLC-MS (Method A): m/z = 602 (M+1); R_t = 5.4 min.

Example 32 (General procedure (D))

4-Dipropylsulfamoyl-N-{3-[4-(1-phenyl-ethyl)-piperazine-1-carbonyl]-naphthalen-2-yl}-benzamide

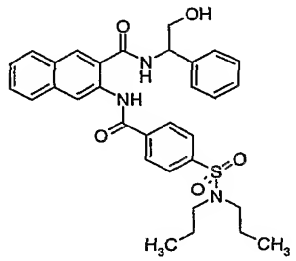


Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 1-(1-phenylethyl)-piperazine in 47 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.85 (t, 6 H) 1.25 (d, J=5.65 Hz, 3 H) 1.51 (m, 4 H) 2.44 (m, 4 H) 3.10 (t, J=7.16 Hz, 4 H) 3.40 (m, J=2.26 Hz, 4 H) 3.56 (m, 1 H) 7.30 (m, 5 H) 7.57 (m, 2 H) 7.96 (m, 5 H) 8.09 (m, J=6.41 Hz, 3 H) 10.59 (s, 1 H); HPLC-MS (Method A): m/z = 628 (M+1); R_t = 3.8 min.

Example 33 (General procedure (D))

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide



Step B: The title compound was prepared from 3-(4-dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid methyl ester and 2-phenylglycinol in 56 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (t, J=7.16 Hz, 6 H) 1.50 (m, 4 H) 3.08 (m, 4 H) 3.75 (m, 2 H) 5.06 (t, J=5.65 Hz, 1 H) 5.20 (q, J=5.28 Hz, 1 H) 7.32 (d, 3 H) 7.49 (d, J=7.54 Hz, 2 H) 7.56 (t, J=7.54 Hz, 1 H) 7.64 (t, J=7.54 Hz, 1 H) 8.01 (m, 6 H) 8.62 (s, 1 H) 9.02 (s, 1 H) 9.42 (d, J=7.91 Hz, 1 H) 12.24 (s, 1 H); HPLC-MS (Method A): m/z = 575 (M+1); R_t = 5.2 min.

PHARMACOLOGICAL METHODS

The following abbreviations are used:

Tris: Tris(hydroxymethyl)aminomethane

GSH: Glutathione

EDTA: Triethanolamine

ATP: Adenosinetriphosphate

LPS: Lipopolysaccharide

Assay (I)

A pure enzyme assay is based on MAPKAP-K2 phosphorylation of a substrate peptide. Purified recombinant human MAPKAP-K2, 0.4-2 unit/ml, is reacted with 30 µM peptide substrate (KKLNRTLSVA) in the reaction buffer (50 mM Tris/HCL pH 7.5, 0.1 % Bovine serum albumin, 5 mM GSH, 0.5 mM EDTA, 100 µM ATP,1 µCi 33P-g-ATP) for 15 min at 30 degrees

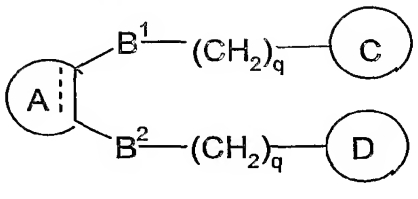
and stopped by adding 13 µl 2 % H_3PO_4. Samples are spotted on to P30 paper, washed extensively in 0.5 % H_3PO_4 and counted by liquid scintillation.

Assay (II)

A whole blood assay has been established to measure the effect of a MAPKAP-K2 inhibitor on LPS induced cytokine production. Rat blood is collected in heparinised vacutainers. Whole blood is diluted 1:1 in RPMI 1640 media and the assay is performed by preincubation for 30 min with compound before addition of 100 ng/mL of LPS for 5 hours. The assay is stopped by centrifugation at 2000 g for 10 min at 4 degrees and the supernatant is collected. The supernatant is assayed for TNFα content by ELISA using a commercial kit from BD Biosciences.

CLAIMS

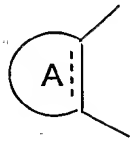
1. A compound of the general formula (I)



(I)

wherein

each q is independently 0 or 1;



is cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused arylcycloalkylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylheteroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroarylene, or fused heteroarylheterocyclylene,

optionally substituted with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34}, wherein

R^{31}, R^{32}, R^{33}, and R^{34} independently of each other are alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^1-O-, R^1-S(O)$_m$-, R^1-O-C(O)-, R^1-C(O)-O-, R^1-C(O)-, $N(R^1)(R^2)$-C(O)-, $N(R^1)(R^2)$-, R^1-C(O)-N(R^2)-$(CH_2)_m$-, $B(OR^1)(OR^2)$-, R^1-O-$(CH_2)_n$-, or $N(R^1)(R^2)$-$(CH_2)_n$-, wherein

R^1 and R^2, independently of each other, are hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

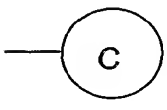
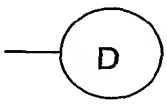
or

R^1 and R^2, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

m is an integer of 0,1, or 2;

n is an integer of 1, 2, or 3; and

 indicates a single bond, double bond or an aromatic bond;

 and 

each independently represent a group selected from the following:
cycloalkyl, heterocyclic, aryl, heteroaryl, fused cycloalkylaryl, fused arylcycloalkyl, fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl,
optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38}, wherein
R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are alkyl, halogen,aralkyl, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^3-O-$(CH_2)_w$-, R^3-S(O)$_v$-, N(R^3)(R^4)-S(O)$_v$-, -R^3-O-C(O)-, R^3-C(O)-O-, R^3-C(O)-, N(R^3)(R^4)-C(O)-, R^3-C(O)-N(R^4)-$(CH_2)_w$, B(OR^3)(OR^4)-, N(R^3)(R^4)-$(CH_2)_w$-, or phenyl optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^5-O-, R^5-S(O)$_s$-, R^5-O-C(O)-, R^5-C(O)-O-, R^5-C(O)-, N(R^5)(R^6)-C(O)-, N(R^5)(R^6)-, R^5-C(O)-N(R^5)-$(CH_2)_t$, B(OR^5)(OR^6)-, R^5-O-$(CH_2)_t$-, or N(R^5)(R^6)-$(CH_2)_t$-, wherein

R^3 and R^4, independently of each other, are hydrogen, halogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, or phenyl optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, N(R^7)(R^8)-, or N(R^7)(R^8)-$(CH_2)_a$-, wherein

R^7 and R^8, independently of each other, are hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, or cycloalkyl;
and
a is an integer of 1, 2, or 3,

or

R^3 and R^4, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

R^5 and R^6, independently of each other, are hydrogen, halogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

or

R^5 and R^6, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

v and s, independently of each other, are an integer of 0,1, or 2; and
w, r and t, independently of each other, are an integer of 0, 1, 2, or 3;

B^1 and B^2, independently of each other, are a linker selected from the group consisting of –C(X)-, –O-C(X)-, -C(X)-O-, -N(R^{15})-C(X)-, -C(X)-N(R^{15})-, -N(R^{15})-S(O)$_w$-, or -S(O)$_w$-N(R^{15})-, wherein

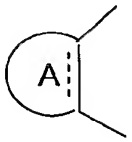
w is an integer of,1, or 2;

X is O, S or H_2; and

R^{15} is hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl or cycloalkyl,

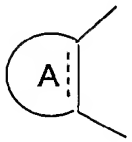
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

2. A compound of claim 1, wherein



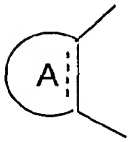
is cycloalkylene, arylene, fused arylcycloalkylene, fused cycloalkylarylene, optionally substituted with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above,

3. A compound of claim 1, wherein



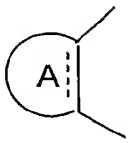
is heteroarylene, heterocyclylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylheteroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroarylene, or fused heteroarylheterocyclylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

4. A compound according to claims 1 or 2, wherein



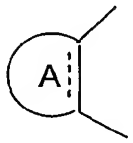
is cycloalkylene, heteroarylene or arylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

5. A compound according to claims 1-3 wherein



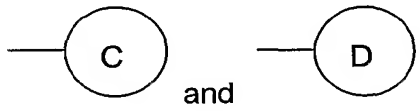
is fused arylcycloalkylene, fused cycloalkylarylene, fused heterocyclylarylene, fused arylheterocyclylene, fused cycloalkylheteroarylene, fused heteroarylcycloalkylene, fused heterocyclylheteroarylene, or fused heteroarylheterocyclylene optionally substited with one or more substituents R^{31}, R^{32}, R^{33}, and R^{34} as defined above.

6. A compound according to claim 1-4 wherein



is phenyl, naphtyl or thienyl.

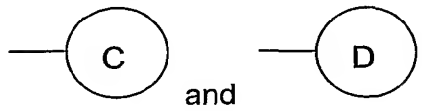
7. A compound according to any of the above claims, wherein



and

each independently represent a group selected from the following:
cycloalkyl, aryl, fused cycloalkylaryl or fused arylcycloalkyl,
optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

8. A compound according to claims 1- 6 wherein

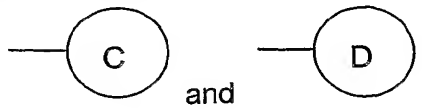


and

each independently represent a group selected from the following:
heterocyclic, heteroaryl, fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl,

optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

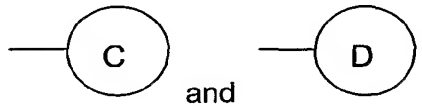
9. A compound according to claims 1- 6 wherein



and

each independently represent a group selected from the following:
heterocyclic, heteroaryl, cycloalkyl or aryl
optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

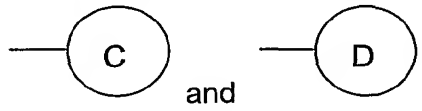
10. A compound according to claims 1-6 wherein



and

each independently represent a group selected from the following: fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heteroarylcycloalkyl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl, fused cycloalkylaryl or fused arylcycloalkyl, optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

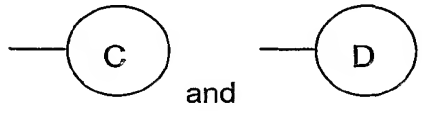
11. A compound according to claims 9 wherein



and

each independently represent a group selected from the following:
aryl or heteroaryl optionally substituted with one or more substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

12. A compound according to claim 11 wherein



and

are selected from phenyl, naphtyl, thienyl, thiazolyl or pyridyl and wherein substituents R^{35}, R^{36}, R^{37}, and R^{38} as defined in claim 1.

13. A compound according claims 1 -12, wherein
R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are alkyl, halogen, aralkyl, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^3-O-$(CH_2)_w$-, R^3-S$(O)_v$-, N$(R^3)(R^4)$-S$(O)_v$-, -R^3-O-C(O)-, R^3-C(O)-O-, R^3-C(O)-, wherein R^3 and R^4, v and w are as defined in claim 1.

14. A compound according to claim 1-13. wherein R^3 and R^4 are independently selected from hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, or
R^3 and R^4, when attached to a nitrogen atom, together with said nitrogen atom form a cycloalkyl or heterocyclyl ring, optionally substituted with one or more alkyl substituents;

15. A compound according to claim 14 wherein R^3 and R^4 are hydrogen or alkyl;

16. A compound according to claims 1-12 wherein R^{35}, R^{36}, R^{37}, and R^{38}, independently of each other, are N$(R^3)(R^4)$-C(O)-, R^3-C(O)-N(R^4)-$(CH_2)_w$, B$(OR^3)(OR^4)$-, N$(R^3)(R^4)$-$(CH_2)_w$-, or phenyl optionally substituted with one or more substituents selected from the group consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, $-NO_2$, R^5-O-, R^5-S$(O)_s$-, R^5-O-C(O)-, R^5-C(O)-O-, R^5-C(O)-, N$(R^5)(R^6)$-C(O)-, N$(R^5)(R^6)$-, R^5-C(O)-N(R^5)-$(CH_2)_t$, B$(OR^5)(OR^6)$-, R^5-O-$(CH_2)_t$-, or N$(R^5)(R^6)$-$(CH_2)_t$-, wherein R^3, R^4, R^5, R^6, w, s and t are as defined in claim 1.

17. A compound according to claims 1-16, wherein B^1 and B^2, independently of each other, are a linker selected from the group consisting of –C(X)-, –O-C(X)-, -C(X)-O-, -N(R^{15})-C(X)-, -C(X)-N(R^{15})-, wherein X is O, S and R^{15} is as defined in claim 1.

18. A compound according to claim 17 wherein B^1 and B^2 independently of each other, are selected from –C(O)-, –O-C(O)-, -C(O)-O-, -N(R^{15})-C(O)- or -C(O)-N(R^{15})-, wherein R^{15} is as defined in claim 1.

19. A compound according to claim 18 wherein R^{15} is hydrogen, hydroxyalkyl, alkyl, alkenyl or alkynyl;

20. A compound according to claim 19 wherein R^{15} is hydrogen or alkyl;

21. A compound according to claim 1, said compound being:
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid methyl ester
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 3-carboxy-naphthalen-2-yl ester
3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid 2-(3-carboxy-naphtaleneoxycarbonyl) naphtyl ester
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid
2-(4-Dipropylsulfamoyl-benzoylamino)-benzoic acid
2-[(4-Dipropylsulfamoyl-benzoyl)-methyl-amino]-benzoic acid
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 2,4,6-trimethoxy-benzylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid 4-methanesulfonyl-benzylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-2-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-3-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (biphenyl-4-ylmethyl)-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid benzylamide
2-(4-methoxy-benzoylamino)-N-(2-thiazolyl)-benzamide
3-(4-Methoxy-benzoylamino)-naphthalene-2-carboxylic acid thiazol-2-ylamide
3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide
Pyridine-2-carboxylic acid [3-(thiazol-2-ylcarbamoyl)-naphthalen-2-yl]-amide
Pyridine-2-carboxylic acid {3-[(naphthalen-1-ylmethyl)-carbamoyl]-naphthalen-2-yl}-amide
3-(4-Dipropylsulfamoyl-benzoylamino)-benzene-2-carboxylic acid (naphthalen-1-ylmethyl)-amide
Pyridine-2-carboxylic acid {2-[(naphthalen-1-ylmethyl)-carbamoyl]-phenyl}-amide
4-({[3-(4-Methoxy-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-[({3-[(Pyridine-2-carbonyl)-amino]-thiophene-2-carbonyl}-amino)-methyl]-benzoic acid methyl ester

4-({[4-(4-Methoxy-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-({[4-(4-Dipropylsulfamoyl-benzoylamino)-thiophene-3-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-[({4-[(Pyridine-2-carbonyl)-amino]-thiophene-3-carbonyl}-amino)-methyl]-benzoic acid methyl ester

3-(4-Dipropylsulfamoyl-benzoyloxy)-naphthalene-2-carboxylic acid

N-(3-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-carbonyl}-naphthalen-2-yl)-4-dipropylsulfamoyl-benzamide

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-2-yl)-amide

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid [1-(4-methoxy-phenyl)-ethyl]-amide

4-({[3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-Dipropylsulfamoyl-N-{3-[4-(1-phenyl-ethyl)-piperazine-1-carbonyl]-naphthalen-2-yl}-benzamide or

3-(4-Dipropylsulfamoyl-benzoylamino)-naphthalene-2-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide

or a pharmaceutically acceptable salt thereof.

22. A compound according to any of claims 1-21, wherein the compound inhibits the MAP-KAP kinase 2, when tested in Assay (I)

23. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 100 µM in the Assay (I), as described in the specification.

24. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 30 μM in the Assay (I), as described in the specification.

25. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 10 μM in the Assay (I), as described in the specification.

26. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 3 μM in the Assay (I), as described in the specification.

27. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 1 μM in the Assay (I), as described in the specification.

28. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 0.3 μM in the Assay (I), as described in the specification.

29. A compound according to claim 22, wherein the compound is an inhibitor of the MAPKAP kinase 2, when tested at a concentration of 0.1 μM in the Assay (I), as described in the specification.

30. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to claims 1-21 together with one or more pharmaceutically acceptable carriers or excipients.

31. The use of a compound according to claims 1-21 for use as a medicament.

32. The use of a compound according to any of the claims 1-21 for the manufacture of a medicament for the treatment of diseases or disorders responsive to inhibition of MAPKAP kinase 2.

33. A method for the treatment and/or prevention of disorders or diseases, wherein a MAP-KAP kinase 2 interaction is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound according to claims 1-21 or a pharmaceutical composition according to the above.

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ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/16 C07C317/32 C07D213/81 C07D277/46 C07D295/18
C07D333/38 C07D409/12 C07D417/12 A61K31/18 A61K31/381
A61K31/426 A61K31/4402 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	H. KARAHASHI, ET AL.: "A selective inhibitor of p38 MAP kinase, SB202190, induced apoptotic cell death of a lipopolysaccharide-treated macrophage-like cell line, J774.1" BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1502, no. 2, 18 October 2000 (2000-10-18), pages 207-223, XP004277003 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL ISSN: 0925-4439 page 217, left-hand column, line 4 - line 26 ---	1-33
A	US 2003/078432 A1 (M.A. LETAVIC, ET AL.) 24 April 2003 (2003-04-24) paragraph '0317! - paragraph '0318!; claim 1 --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2004	16/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/083622 A (LEO PHARMA) 24 October 2002 (2002-10-24) page 25, line 17 - line 18	1-33
X	Y.K. YEE, ET AL.: "N2-Aroylanthranilamide inhibitors of human factor Xa" JOURNAL OF MEDICINAL CHEMISTRY., vol. 43, no. 5, 9 March 2000 (2000-03-09), pages 873-882, XP002186965 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DE, US ISSN: 0022-2623 tables 1-6	1,2,4,6, 7,9, 11-15, 17-20, 22-31
X	P. GRAMMATICAKIS: "Contribution ä l'étude de l'absorption dans l'ultraviolet et le visible des anilines orthosubstituées. IV. o-Amino- et o-acylamino-benzoylarylamines" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, 1962, pages 487-496, XP002289833 SOCIETE FRANCAISE DE CHIMIE, PARIS, FR pages 494-495, compounds 35-49	1,2,4,6, 7,9, 11-13, 17-20, 22-29
X	W. WASMER: "Über die Ultraviolettabsorption einiger Salicylsäureabkömmlinge und verwandter Verbindungen" CHEMISCHE BERICHTE, vol. 82, 1949, pages 342-348, XP002289834 VERLAG CHEMIE, WEINHEIM, DE page 348, lines 8-10	1,2,4,6, 7,9,11, 12, 17-20, 22-29
X	E. CLAR, ET AL.: "Zur Kenntnis mehrkerniger aromatischer Kohlenwasserstoffe und ihrer Abkömmlinge, II. Mitteil.: Das 'Naphtho-2',3':1,2-anthracen!, seine Homologen und Oxydationsprodukte" BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 62, 1929, pages 940-950, XP002289835 VERLAG CHEMIE, WEINHEIM, DE compounds I-III	1,2,4,6, 7,9, 11-13, 17,18, 22-29
X	J. ZAVADA, ET AL.: "Silver perchlorate promoted reactions: arylmethylation of aromatics by bromomethylarenes" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 41, no. 6, June 1976 (1976-06), pages 1777-1790, XP002289836 ACADEMIC PRESS, LONDON, GB compounds VIIa-d	1,2,4,6, 7,9, 11-13, 17,18, 22-29

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ational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. LEPAGE, ET AL.: "Carbocyclisation et hétérocyclisation de dérivés orthodibenzylés, par action du soufre" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 15, October 1978 (1978-10), pages 1185-1191, XP002289837 HETEROCORPORATION, PROVO, US compounds 1-6,13,14,17-20,23,24,28-30,35 ---	1-7,9, 11,12, 17,18, 22-29
X	R.A. ABRAMOVITCH, ET AL.: "Thermal decomposition of o- and p-benzenedisulphonyl azides in benzene, cyclohexane, cyclohexene, and tetracyclone" JOURNAL OF ORGANIC CHEMISTRY, vol. 40, no. 7, 4 April 1975 (1975-04-04), pages 883-889, XP002289838 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DE, US compounds 2,21 ---	1,2,4,6, 7,9, 22-29
X	D.W.H. MACDOWELL, ET AL.: "Reaction of thiophene-2,3-dicarbonyl chloride with aluminium chloride and benzene" JOURNAL OF ORGANIC CHEMISTRY, vol. 42, no. 23, 11 November 1977 (1977-11-11), pages 3717-3720, XP002289839 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DE, US compound 4 ---	1,3,4,6, 8,9,11, 12,17, 18,22-29
X	A. BÖHM, ET AL.: "Electron-transfer induced valence isomerisation of 1,2-distyrylbenzene" TETRAHEDRON LETTERS, vol. 33, no. 5, 28 January 1992 (1992-01-28), pages 611-614, XP002289840 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL compound 8 ---	1,2,4,6, 7,9,11, 12,17, 22-29
X	G. GÖNDÖS, ET AL.: "2-Substituted hexahydroacylanthranils: synthesis and selective reactions with amines" MONATSHEFTE FUR CHEMIE, vol. 127, no. 11, November 1996 (1996-11), pages 1167-1171, XP002289841 SPRINGER VERLAG, WIEN, AT compounds 8a,8b,9a,8b ---	1,2,4,7, 9,11,12, 17-20, 22-29

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INTERNATIONAL SEARCH REPORT

ational Application No
PCT/DK2004/000301

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 258 162 A (E.H. NORTHEY, ET AL.) 7 October 1941 (1941-10-07) example 1 ---	1,2,4,6, 7,9, 11-16, 22-29
X	R.M. PICCIRILLI, ET AL.: "New compounds: isoquinoline derivatives as simple emitine models" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 67, no. 5, May 1978 (1978-05), pages 740-742, XP002289842 AMERICAN PHARMACEUTICAL ASSOCIATION, WASHINGTON, DC, US compound XIII -----	1,2,4,6, 8-11,17, 22-29

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ternational application No.
PCT/DK2004/000301

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 33 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003078432 A1	24-04-2003	BR 0201087 A	27-05-2003
		CA 2379903 A1	04-10-2002
		EP 1247810 A1	09-10-2002
		JP 2002308872 A	23-10-2002
WO 02083622 A	24-10-2002	WO 02083622 A2	24-10-2002
		US 2003073832 A1	17-04-2003
US 2258162 A	07-10-1941	NONE	